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Election
8/22/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

COFFIN et al.

Atty. Ref.: 117-340

Group Art Unit: 1648

Serial No.: 09/762,098

Examiner: Li

Filed: February 2, 2001

For: CELL LINES FOR THE PROPAGATION OF MUTATED HERPES VIRUSES

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August 16, 2002

RESPONSE

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

Sir:

This is in response to the Office Action dated May 16, 2002, in the above, the period for response having been extended up to August 16, 2002, by submission of the required petition and fee herewith.

In response to the Examiner's requirement for restriction, Applicants elect, with traverse, the subject matter of Group I, claims drawn to a process for propagating a mutant herpes virus and a composition prepared by the process (claims 1-12 and 27). With regard to the election of species, the applicants further elect species (1), Equine herpes virus gene 12 and species (b) HSV ICP4.

The requirements for restriction are traversed. At the outset, the Examiner's reasoning as to why the inventions listed as Groups I to VI do not

relate to a single general inventive concept under PCT Rule 13.1 is, with due respect, not believed to be well founded. All claims of the present application share a special technical feature, i.e. all claims relate to the production of a herpes simplex virus which lacks the functional VP16 gene in a mammalian cell, wherein the VP16 is supplied *in trans* from the VP16 transfected cell line and the VP16 gene supplied *in trans* is unable to undergo homologous recombination with the VP16 gene in the virus. This technical feature is not taught or suggested in any of the cited art.

Weinheimer *et al* describes a process for propagating an HSV-1 in which the entire VP16 open reading frame is deleted using a cell line transfected with HSV-1 VP16 to supply the VP16 protein *in trans*. Weinheimer *et al* also describes an experiment in which the cell line transfected with the VP16 gene of HSV-1 is used to propagate an HSV-2 containing a temperature sensitive mutation in the VP16 gene (the ts2203 mutation). Weinheimer *et al* does not, however, disclose the production of a herpes simplex virus having a mutation in the VP16 gene using a VP16 transfected cell line, wherein the VP16 gene in the transfected cell line is unable to undergo homologous recombination with the VP16 gene in the virus.

In the first process disclosed in Weinheimer *et al*, the HSV-1 being propagated does not have a mutation in its endogenous VP16 gene because it simply lacks the entire VP16 open reading frame. In the second experiment

performed by Weinheimer *et al*, the HSV-2 being propagated has a temperature sensitive mutation in the VP16 gene and no homologous recombination was observed. However, Weinheimer *et al* clearly expected that the HSV-1 VP16 gene in the cell line would be able to undergo homologous recombination with the HSV-2 VP16 gene in the virus (page 260, lines 30-35 of the Results section). The HSV-2 VP16 gene shares a 76% overall sequence identity with the HSV-1 VP16 gene and in the VP16 open reading frame this rises to 84% sequence identity (Cress and Triezenberg, 1991, Gene 103: 235-238, page 237 lines 23 to 26). Homologous recombination can occur between two nucleotide sequences sharing this level of homology. Therefore, the experiment described in Weinheimer *et al* is distinct from the process of claim 1 of the present application.

Weinheimer *et al* does not teach that it may be desirable to exclude the possibility of homologous recombination occurring between an endogenous viral gene and the gene supplied *in trans* using a complementing cell line. Thus, Weinheimer *et al* does not teach or suggest that it would be desirable to use two different VP16 genes in the cell line and virus, which genes are incapable of undergoing homologous recombination with each other.

Lachmann *et al* teaches that it is desirable to prevent homologous recombination between the vector and viral sequences contained within the complementing cell during that propagation and teaches that to do this it is

necessary to ensure that all sequences that have been inserted in the cell line have been deleted from the virus.

VP16 complementation, however, presents a specific problem that cannot be solved simply by deleting the endogenous VP16 sequences. VP16 is a multi-functional protein. It is desirable to eliminate the transactivation function of the VP16 protein by mutation in herpes virus vectors to provide a virus that is safe for use as a vector. However, the VP16 gene can not be deleted in its entirety because VP16 has an essential structural function. Thus, the solution suggested in Lachmann *et al* for preventing homologous recombination by deleting the endogenous gene sequences can not be applied when the gene being complemented is VP16.

The Applicants have solved this problem by using a VP16 gene in the complementing cell line that shares no more than 50% sequence identity with the VP16 gene in the virus being propagated (page 7 lines 26 to 31 of the specification). This can be achieved, for example, using a VP16 homologue from a different viral species such as equine herpes virus or from bovine herpes virus.

Neither Weinheimer *et al* or Lachmann *et al* teach or suggest that a VP16 gene homologue having a suitably low sequence identity to prevent homologues recombination occurring with the endogenous gene (i.e. as little as 50%) will be capable of complementing the function of the endogenous gene. Thus, a novel feature of claim 1, i.e. that the complementing VP16 gene in the cell line is unable

to undergo homologous recombination with the endogenous gene, is not taught or suggested in the prior art and all claims of the present application share a common inventive technical feature. Accordingly, it is submitted that the inventions listed as Groups I to VI relate to a single inventive concept.

Respectfully, it is submitted that a complete search of the art relating to Group I would necessarily encompass the subject matter of Groups II to VI, and especially that of Group VI which is a virus produced by a process encompassed by the Group I claims. Accordingly, the applicants respectfully submit that no undue burden would be placed on the Examiner by examining the subject matter of the Examiner's Groups I-VI in the same application.

Should the Examiner deny the applicants' request to withdraw the restriction requirement, petition is hereby made by Applicants to the Commissioner to invoke his supervisory authority and to have the restriction requirement withdrawn. Submitted herewith is a Contingent Petition Under Rule 181 for that purpose.

Respectfully submitted,

NIXON & VANDERHYE, P.C.

By_____
B. J. Sadoff
Reg. No. 36,663

BJS:plb

1100 North Glebe Road
8th Floor
Arlington, Virginia 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100